REMARKS

Claims 1-20 are pending in this application. Claims 5 and 13 have been withdrawn as drawn to the non-elected invention. Claims 1-4, 6-12, and 14-20 are currently under examination in the present application. Claims 1-4, 6-12, and 14-20 have been rejected. Claims 1, 2, 9, 10, 16 and 18-20 have been amended, and claim 17 has been cancelled. No new matter has been added. Applicants reserve the right to re-file this subject matter in a continuation or divisional application filed during the pendency of this application.

Specification

The specification was objected to for containing an embedded hyperlink. Applicants have amended the specification to not contain the embedded hyperlink, thereby rendering the objection moot.

Sequence Rules Compliance

The application was objected to for containing nucleotide sequences not in compliance with 37 CFR § 1.821 through 1.825. Applicants have amended the specification to include the appropriate sequence identifiers with these nucleotide sequences and have submitted herewith a revised Sequence Listing in paper and Computer Readable Form (CRF) which includes these new sequence identifiers and their respective sequences. Applicants contend that the application is in compliance with 37 CFR § 1.821 through 1.825, and accordingly request withdrawal of the objection.

Rejection under 35 U.S.C. § 112(2)

Claims 16-20 were rejected under 35 U.S.C. § 112, second paragraph as indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 was rejected for the recitation of "defining a set of diversely modified ligands based on incremental pharmacophore changes." Specifically the examiner stated that the specification nor the claims set forth what attributes are considered "defining" and the words "diversely," "modified" and "incremental" are each relative words that the specification nor the claims provide no distinct teaching as to when the parameters of these words are exceeded, and thus the artisan could not be reasonably sure that he or she were practicing the invention.

Applicants contend that these terms are readily understood by those of skill in the art. The term pharmacophore was first defined by Paul Ehrlich in 1909 as "a molecular framework that carries (phoros) the essential features responsible for a drug's (pharmacon) biological activity" (Ehrlich. *Dtsch. Chem. Ges.* 1909, 42: p.17). In 1977, this definition was updated by Peter Gund to "a set of

structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity" (Gund. *Prog. Mol. Subcell. Biol.* 1977, 5: pp 117–143), [Wikipedia, Osman F. Güner (2000) *Pharmacophore Perception, Development, and use in Drug Design*].

A pharmacophore element is therefore one of these structural features that is recognized at a receptor site, i.e., a component of the pharmacophore. Together, the ensemble of pharmacophore elements in a molecule comprise the major binding interactions to the protein receptor. A selection of references from the scientific literature discussing examples, definition, and use of the term pharmacophore element is provided herewith (Ablordeppey *et al.*, Nassif-Makki *et al.*, Malaska *et al.*, Kozikowski *et al.*). Incremental changes to this pharmacophore, by common English usage, means stepwise or gradual alterations. In the context, an "incremental pharmacophore element change" means an alteration to the pharmacophore achieved by changing single pharmacophore elements one at a time. Each iteration of a pharmacophore element change manifests itself in a new chemical structure, i.e., a new ligand. Thus, relative to the initial template ligand, the derived ligand is therefore a "*modified* ligand based on incremental pharmacophore element change". When a collection of ligands is designed and collected/prepared, i.e., "defined", by this method, and in such as way that the resulting structures are substantially different from one another, it may be said that one has "defined a set of diversely modified ligands based on incremental pharmacophore element changes". By definition, the difference in structure between any two ligands in the collection, or set, will be necessarily limited to one portion or one section of the molecule, i.e., one pharmacophore element. However, when considered as a group, the structural differences among the members of the group of ligands are significant. One would say that they are "diversely modified".

Further clarification of the common-usage terms "define", "set", "diversely", and "modified" may be found in standard English dictionaries.

An artisan would know that he or she is practicing the claimed invention if the artisan is:

(a) Defining (designing and collecting/preparing) a set of diversely modified ligands

and

(b) These ligands are defined based on one-at-a-time (incremental) changes in individual components (elements) of the pharmacophore.

Requirements (a) and (b) are clearly and explicitly stated in the claim and within the specification (see page 40, lines 3-31). Definitions of the terminology are available in the medicinal chemistry literature and/or in common English usage as indicated in standard dictionaries. Indeed, an independent artisan would be able to examine such a candidate set of ligands and determine whether or not they satisfy these criteria.

Claim 16 was rejected for the recitation of "querying the receptor polypeptides." Specifically the examiner indicated that the claims do not specify what questions or inquiries are meant to be encompassed by the query.

Applicants assert that the gerund phrase "querying the receptor polypeptides" is modified by the prepositional phrase "for gene modulation, or ligand domain binding, or both". Therefore, the questions, or inquiries, encompassed by the query are:

(a) "how and/or to what extent is the gene modulated?", and

(b) "to what extent is the ligand binding domain bound?"

In the overall context of the present gene regulation patent application, "gene modulation" means the change in direction and magnitude of expression of the gene, compared to expression of the gene in the absence of ligand. The query is conducted by performing a biological assay. The measurement actually made in such an assay is typically the colorimetric output of an enzymatic reaction directly proportional (but not necessarily a linear relationship) to the quantity of protein generated after transcription of the gene into RNA and subsequent translation of the gene into a protein. Thus, the quantity of protein generated is in turn related to the quantity of ligand present, the potentiating propensity of the ligand, and the binding affinity of the ligand for the receptor. These relationships are generally monotonic but do not necessarily adhere to well-defined mathematical equations. Other assay outputs such as the magnitude of antibody binding are also possible. As discussed here, assays for gene expression and their relationship to ligand actuation are well-described in the scientific literature.

"Binding to the ligand binding domain" indicates the thermodynamic affinity of the ligand for the pocket in the receptor that, relative to other protein binding surfaces, has a particularly complementary shape and size to the ligand. Often, these pockets, or ligand binding domains, are described by protein crystal structures or can be inferred from primary amino acid sequences. One measures the "extent of binding to the ligand binding domain" typically by performing a competitive binding assay in which a known, previously-characterized ligand is displaced by the test candidate ligand in a competitive binding assay. The magnitude of displacement is quantitatively measured. Competitive binding assays of this type, their purpose and their use are defined and well-characterized in the scientific literature.

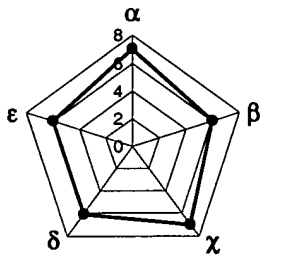
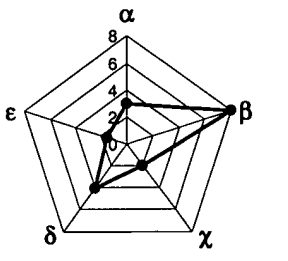
Thus, one "queries the receptor polypeptides" for "the extent of gene modulation", i.e., change in direction and magnitude of gene expression, and "binding" to the "ligand binding domain" by performing gene expression assays and ligand binding assays. The output is quantitative and comparative among ligands.

Claim 16 was rejected as the examiner stated that the relationship between "determining the orthogonality of the receptor polypeptide/ligand combination" and "defining a subset of ligands with diverse gene modulation properties" is unclear, particularly with how the first accomplishes the second.

Applicants contend that "the orthogonality of the receptor polypeptide/ligand combination" indicates the relative sensitivity of a series of receptors to a series of ligands. A strict definition is provided in the specification, page 26, lines 3-16. The scientific literature further defines and exemplifies ligand/receptor orthogonality and Applicants have provided copies of a few of these references herewith (Belshaw *et al.*, Pierce *et al.*, Peet *et al.*, Doyle *et al.*).

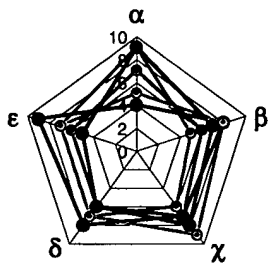
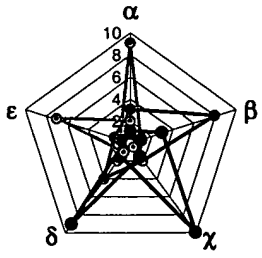
"Diverse gene modulation properties" *with respect to a single ligand* means that the potency, or the ability to potentiate gene expression, of a given ligand with respect to a series of receptors differs widely. The left-hand side of Figure 1 shows a ligand with homogenous or non-diverse gene modulation properties; in contrast, the right-hand side shows a ligand with diverse gene modulation properties.

Figure 1.

A ligand with *Non-diverse* **gene modulation properties**	**A ligand with** *Diverse* **gene modulation properties**
	

"Diverse gene modulation properties" with respect to multiple ligands means that the profile of potency differs substantially for a given ligand within a set of ligands, *taken one at a time but considered together as a group*, against a given set of receptors. The left-hand side of Figure 2 shows a set of ligands with non-diverse gene modulation properties; in contrast, the right-hand side shows a set of ligands with diverse gene modulation properties. The right-hand figure also depicts a 5-channel switch with a high degree of orthogonality.

Figure 2

Subset of Ligands with *Non-diverse* Gene modulation Properties	**Subset of Ligands with *Diverse* Gene modulation Properties**
-log(EC50) **Ligands A-E on Receptors α–ε**	**-log(EC50)** **Ligands A-E on Receptors α–ε**
	

Therefore "defining a subset of ligands with diverse gene modulation properties" means to (a) perform gene regulation assays on a group of ligands with respect to a group of receptors, (b) determine the relative ability to potentiate gene expression for each ligand against each receptor, (c) compare the expression profiles and (d) select combinations of receptors and ligands which have highly asymmetric selectivity. One method among many to visualize such relationships are radial graphs as depicted. A more thorough explanation of the method to identify such relationships is given in Appendix 2.

Hence, the relationship between "determining the orthogonality of the receptor polypeptide/ligand combination" and "defining a subset of ligands with diverse gene modulation properties" is one of *sequential steps in a process*. One must perform the first step in order to identify *single* ligands which are orthogonal with respect to *receptor pairs*. (alternatively, one may identify *single* receptors which are orthogonal with respect to *ligand pairs*). Then, as a second step, one combines the observations of orthogonality concerning single ligands to generate a superset of observations concerning multiple ligands. (Alternatively, one may combine the observations of orthogonality concerning single receptors to generate a superset of observations concerning multiple receptors).

Stated another way, "determining the orthogonality of the receptor polypeptide/ligand combination" manipulates assay data to discover fundamental ligand-receptor relationships, while "defining a subset of ligands with diverse gene modulation properties" manipulates the resultant fundamental ligand-receptor relationship data to discover multiple ligand-multiple receptor relationships.

The second step is not the accomplishment or the result of the first step (as the examiner's question seems to suggest). Rather, the second step is built on the foundation of and made possible by the first step. This type of relationship is one of the standard English uses of the preposition "to" as found in claim 16(e) linking the two phrases "determining the orthogonality of the receptor polypeptide/ligand combination" and "defining a subset of ligands with diverse gene modulation properties".

In view of the foregoing and as the "requirement to 'distinctly' claim means that the claim must have a meaning discernible to one of ordinary skill in the art when construed according to correct principles" [see *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1366, 71 USPQ2d 1081, 1089 (Fed. Cir. 2004)], Applicants contend that claims 16-20 are definite and satisfy the requirement of 35 U.S.C. 112, second paragraph, as the components of the terms and phrases in the claims have well recognized meanings, which allow the skilled artisan to infer the meaning of the entire phrase with reasonable confidence. Accordingly, withdrawal of the rejection is respectively requested.

Rejection under 35 U.S.C. § 112(1)

Claims 1-4, 9-12 and 14-20 were rejected under 35 U.S.C. § 112, first paragraph, because the specification while enabling for cell-based multiple inducible regulation systems, does not provide enablement for virally based multiple inducible regulation systems.

Specifically, the examiner suggests that the claims are directed to very complex systems requiring the use of multiple and distinct expression and regulatory vectors and cites one review article by Fussenegger who suggests "the VgEcR based technology is genetically complex and requires simultaneous expression of two proteins which may complicate or prevent its use in certain viral delivery systems and autoregulatory configurations." Fussenegger only suggests a complication in the use of a specific system, VgEcR, in certain viral delivery systems, without citing any data or references to support his assertion. Applicants have submitted herewith two peer-reviewed journal articles (Hoppe *et al.* and Holt *et al.*) pre-dating Fussenegger and the priority date of the present application which demonstrates that ecdysone receptor-based viral vectors have been made and used by those of skill in the art. Accordingly, it is well known to those of skill in the art not only how to make viral vectors, package the viral vectors and transduce cells with the viral particles, but also how to make and use ecdysone receptor-based viruses.

Applicants contend that those of skill in the art already know how to make and use ecdysone-receptor-based viral vectors. Accordingly, Applicants submit that claims 1-4, 9-12, 14-16 and 18-20 satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. Withdrawal of the rejection is respectively requested.

Claims 1-4, 9-12 and 14-20 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Specifically, the examiner suggests that the claims encompass viral based multiple inducible gene regulation systems, yet the specification provides no description of such nor any teaching that would enable one skilled in the art to possess such. For the reasons discussed above, applicants contend that it is well known to those of skill in the art how to make viral vectors, package viral vectors and transduce host cells with the viral particles. As demonstrated in the two articles provided herewith, those of skill in the art know how to make and use ecdysone-receptor based viral vectors and viruses. The specification describes on page 13 the vector systems that may be used in accordance with the present invention. Specifically the inventors describe the use of human or animal viruses, such as vaccinia or adenovirus or insect viruses, such as baculovirus. On page 14, lines 7-10, the inventors describe further additional viruses that may be used, such as retroviruses, adeno-associated viruses, and herpes simplex virus. On page 14, lines 28-32, the inventors describe how these vectors may be introduced into host cells and provide the appropriate references for these routine methods.

Those of skill in the art know how to make and use, have made and used, ecdysone receptor-based viral vectors and viruses. This is evident by the articles provided herewith. Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. What is conventional or well known to one of ordinary skill in the art need not be described in detail in the specification. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-84, 231 USPQ 81, 90 (Fed. Cir. 1986). If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

Applicants contend that those of skill in the art already know how to make and use ecdysone-receptor-based viral vectors. Accordingly, Applicants submit that claims 1-4, 9-12, 14-16 and 18-20 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. Withdrawal of the rejection is respectively requested.

Rejection under 35 U.S.C § 102(b)

Claims 1, 2, 4, 6-10, 12, and 14-20 were rejected under 35 U.S.C. § 102(b) as anticipated by Moradopour *et al.* The examiner suggests that Moradopour *et al.* disclose a multiple inducible gene

modulation system comprising a plurality of individually operable gene modulation systems wherein each individually operable gene modulation system comprises: i) one or more polynucleotides encoding a receptor complex comprising A) a DNA binding domain, B) a ligand binding domain, C) a transactivation domain; ii) a ligand and iii) a polynucleotide comprising A) an exogenous polynucleotide and B) a response element, wherein the exogenous polynucleotide is operatively linked to the response element and binding of the response element in the presence of ligand results in activation of the polynucleotide and each system is orthogonal.

Moradpour *et al.* describe co-expression of a tetracycline- and an ecdysone-regulated gene expression system. The claims, as amended, are directed to multiple gene regulation systems, wherein the ligand binding domains are from nuclear receptors. Moradopour *et al.* describe one ligand binding domain from a nuclear receptor and another ligand binding domain that is not a nuclear receptor.

In regards to the rejection of claims 16-20, the examiner suggests that the procedures disclosed by Moradopour *et al.* appear to read on the claims given their broadest possible interpretation. Applicants content that the claims, as amended, are directed to method to develop a multiple gene regulation system, wherein the receptor polynucleotides comprise a ligand binding domain from a nuclear receptor.

Moradopour *et al.* fail to teach or disclose Applicants' invention. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d, 1913, 1920 (Fed. Cir. 1989). The prior art fails to provide each and every element set forth in the present claims for the reasons set forth above.

Thus, Applicants maintain that the cited prior art fails to teach or disclose the present invention as required to set forth anticipation of the claims. Accordingly, withdrawal of the rejection is respectfully requested.

In view of the foregoing amendments and remarks, Applicants submit that this application is in condition for allowance. Therefore, Applicants respectfully request reconsideration and withdrawal of all of the above rejections.

Respectfully submitted,

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